IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
10/736,084	12/15/2003	Joseph C. Walsh	2003P88074US

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REMARKS

Applicant hereby authorizes the PTO to charge any and all necessary fees due, or provide reimbursements of excessive fees paid, to deposit account No. 19-2179.

Entry of this Amendment is respectfully requested. No new matter is added by the Amendment.

Claims 1-32 are pending in this application; with Claims 33 and 34 having been canceled in a previous response to a Restriction Requirement.

Claim Rejections- 35 USC § 103

On page 3 of the Office Action, the Examiner maintained the rejection of Claims 1-32 under 35 U.S.C. 103(a) as being unpatentable over Fox et al (The Journal of Organic Chemistry, 1968, 33(4), 1592-99) in combination with Miller et al (J. Org. Chem. 1963, 28, 936-41).

The Examiner cites the factual inquiries under *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a):

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Applicants respectfully traverse the Examiner's rejection of Claims 1-32 over the cited art and hereby incorporate by reference Applicants' response and remarks dated April 17, 2007.

Rejection of Compounds of Claim 21, Claim 29, and Claim 30:

On page 4 of the Office Action, the Examiner rejected Claim 21 and Claim 30 as being obvious, alleging:

> "Fox et al teach the preparation of compound 8, a thymidine derivative (page 1593, Figure 2). This compound is structurally the same as the compounds in instant claims 21 and 30 except that the 5' hydroxyl group is protected in the instant compound." (Emphasis added)

Applicants respectfully traverse the Examiner's general allegation that, in hindsight and in view of Applicants disclosure, because a structurally related and known compound can be converted to any other different and new compound, in the absence of any teaching, suggestion or motivation, the new compound is simply obvious.

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1. Determining the scope and contents of the prior art.

The bicyclic compound 8 taught by Fox et al is an intermediate containing a 5' hydroxyl derivative of thymidine that was prepared by the hydrolysis of compound 4. See figure 2, page 1593. In addition, as an intermediate that is useful for the preparation of other biological active compounds, such as compound 6 as noted by the Examiner, Fox et al teach that according to the reaction process, compound 8 must be formed as the free 5' hydroxyl derivative of thymidine under the hydrolysis condition such that the process for the reaction of compound 8 with liquid ammonia forms the desired compound 6. Fox et al further teach that various derivatives of the tricylic compound 6 may then be prepared from compound 8. Fox et al teach that the preparation of compounds of biological interest such as compound 6, may be prepared by using intermediate compounds such as 8.

Accordingly, one skilled in the art, in viewing the teaching of Fox et al, would have been motivated to prepare the intermediate compound 8 with the 5' unprotected hydroxyl derivative and further employ the 5' unprotected hydroxyl derivative to synthesize the tricyclic compound 6. That is, the teaching of Fox et al suggests to one skilled in the art can readily prepare the 5' unprotected compound from the starting compound 4 to prepare biological active compound 6.

The Examiner also rejected the trityl enolate compound recited in Claim 29, citing Miller et al who disclose a thymidine derivative II (page 936, Figure 1) as being "structurally very close" to the compound claimed in Claim 29, "except that the carbonyl group in the base is not present as an enolate," and the Examiner comments that "such an enolate structure is an important intermediate taught by Fox (above)." On page 5 of the Office Action, the Examiner further notes that

> "Fox teaches the conversion of the anhydro intermediate 4 to the derivative 5, may not be the same as the compound obtained in step (c) of instant claim 1 but is similar. A derivative that is structurally similar to the compound in step (a) of claim 1 (the protected derivative) is taught by Miller (structure III of Miller in Figure 1). Even though the structure of the anhydro derivatives are slightly different in both Fox and Miller one of ordinary skill in the art will recognize that the sequence of steps can be applied to make the compound in instant claim 1 via the steps as instantly claimed with slight modifications. Such a modification based on the prior art is well within the purview of one of ordinary skill in the art.
>
> Based on the teachings of the prior art, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make compounds as claimed in instant claims 21-30 via the process as claimed in instant claims 1-20 since structurally very close compounds as instantly claimed and steps for the same are seen to be taught in the prior art." (Emphasis added)

2. Ascertaining the differences between the prior art and the claims at issue.

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Fox et al do not teach nor suggest the method, the purpose nor the motivation for adding a hydroxyl protecting group to the 5' hydroxyl group of compound 8 to form the compound as recited in Claim 21 and 30, as such an extra step in the process is not useful, feasible nor efficient for the formation of the tricyclic compound 6.

More importantly, the sequence employed by Fox et al. requires that initially the 5' leaving group be in place so that the tricyclic ring forms between the base and the 5' position. This is contrary to the instant process which requires that there be in place the '5 *protecting* group and that the 3' position, alone, has the leaving group so that it alone is free to form the tricyclic ring with the base. Once the enol ether is formed, in the instant process, *then* the 3' substitution with the radiolabel leaving group occurs. Both steps require that the 5' position be protected. This is an important distinction.

In the present application, the radiolabel leaving group at the 3' position is incorporated *uniformly and in the last step* of the synthesis. Thus, the 3' position must be the last possible site available for substitution with the radiolabel. The process of Fox et al. would make it impossible to incorporate the radiolabel leaving group at the 3' position alone since, in the Fox et al. process, after the enol ether is formed, both the 5' position and 3' position would be available for substitution with the radiolabel leaving groups.

Because the process of Fox teaches a series of steps that would prevent the compounds of the instant claims from being formed, the process of Fox et al. necessarily teaches away from the process and the compounds of the present application.

Thus, neither Fox et al alone or Fox et al in combination with Miller et al, teach or make obvious the compounds recited in Claims 21, 29 and 30, and any such combination of the use of the compounds of Miller et al with the process disclosed by Fox et al would not have any expectation of success in the preparation of the recited compounds.

3. Resolving the level of ordinary skill in the pertinent art.

Applicants respectfully note that the application of the obviousness factors outlined in Graham v. John Deere Co. is an important test that is applicable to a broad range of different inventions and technologies, and in Graham, these obviousness factors were specifically addressed with respect to a clamp for a shank plow for plowing dirt. On the other hand, the present application relates to the synthesis of compounds containing radioactive isotopes for use in positron emission tomography (PET) for diagnostic imaging techniques.

Applicants respectfully note that the standard for obviousness in ascertaining the differences between the prior art and the claimed invention is significantly different when applied to chemical compounds and their use in chemical synthesis and as biologically active agents than the standards that are employed for mechanical inventions, such as a clamp on a plow for plowing dirt.

"For a chemical compound, a prima facie case of obviousness requires 'structural similarity between claimed and prior art subject matter ... where the prior art gives reason or motivation to make the claimed compositions.'" *In re Dillon,* 919 F.2d 688,

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692 (Fed. Cir. 1990) *(en banc)*. "Because of the unpredictable nature of chemical reactions, a newly-synthesized compound may be very similar in structure to known and existing compounds and yet exhibit very different properties. Further, many such new compounds are obvious in the sense that any competent chemist could have synthesized them *if requested or motivated to do so*." 2 Donald S. Chisum, Chisum on Patents §5.04[6] at 5-429 (2000) (emphasis added).

Accordingly, one skilled in the art examining the disclosure of Fox et al would have been motivated to simply use the free 5' hydroxyl compound 8 to prepare various biologically active compounds such as the tricyclic compound 6, and would not have been motivated to prepare a derivative of compound 8 to form the 5' hydroxyl protected compounds recited in Claim 21 and Claim 30. That is, the intermediate compounds taught by Fox et al are different, the process is different and the resulting products formed form this process is significantly different from the compounds recited in Claim 21 and Claim 30.

As stated above, the unpredictable nature of the chemical reactions and the resulting compounds and intermediates prepared from these reactions is particularly pronounced, Applicants respectfully assert that, the Examiner's observation that the thymidine derivative II (page 936, Figure 1) as being "structurally similar," or "structurally very close" to the compound claimed in Claim 29; and that the structure of Claim 1 in the present application is "slightly different" are not the appropriate standards for establishing a *prima facie* case of obviousness. In addition, the Examiner cited the process of Fox et al for the conversion of compound 4 to compound 5, suggesting that the process is "the same as the compound obtained in step (c) of instant claim 1." However, as detailed above, the process taught by Fox et al is significantly distinct from the process of Claim 1 of the present application, because the intermediates are different, the process step and reagents used are different, and the resulting products taught by Fox et al is also different than those recited in Claim 1 of the present application.

The Examiner further states that "[e]ven though the structure of the anhydro derivatives are slightly different in both Fox and Miller one of ordinary skill in the art will recognize that the sequence of steps can be applied to make the compound in instant claim 1 via the steps as instantly claimed with slight modifications. Such modification based on the prior art is well within the purview of one of ordinary skill in the art." Applicants respectfully requests that the Examiner consider that what might be obvious in hindsight of the invention would not necessarily have been obvious at the time of the invention.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The extraordinary lapse in time between the publication dates of the cited art (Fox published in 1968 and Miller in 1963), and the application date of the instant invention, alone indicates that the processes and the compounds prepared from the processes of the present application were not made obvious by the cited art of record. Furthermore, the great utility of the compounds of the present application coupled with this distance in time

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only highlights the nonobviousness of the processes and compounds of the instant invention.

Applicants respectfully traverse the Examiner's characterization of the cited art references as applied to Applicant's invention.

Finally, in addition to the different compounds taught by Fox et al and by Miller et al, neither Fox et al nor Miller et al teach nor suggest the process recited in Claim 1 of the present application.

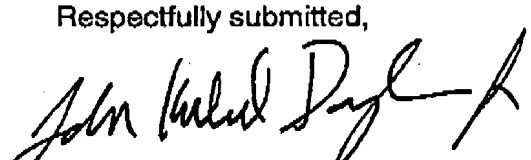
Applicants respectfully request the withdrawal of the 35 U.S.C. 103(a) rejection of Claim 1-32.

Applicants respectfully assert that Claims 1-32 are novel and nonobvious, and allowance of these claims is respectfully solicited. The present application is believed to be in prima facie condition for allowance, and an early action to that effect is respectfully solicited.

In view of the foregoing amendments and remarks, Applicant submits that all of the claims are in proper format and are patentably distinct from the prior art of record and are in condition for allowance.

The Examiner is invited to contact the undersigned at the telephone number listed below with and questions concerning this application.

Respectfully submitted,



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